IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Martin et al.
Application No. 10/607,598
Filed: June 27, 2003
Confirmation No. 7617
For: METHOD FOR THE TREATMENT OF MULTIPLE SCLEROSIS
Examiner: Jegatheesan Seharaseyon
Art Unit: 1646
Attorney Reference No. 4239-66190-01

CERTIFICATE OF MAILING

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DECLARATION OF DRS. MARTIN AND MCFARLAND UNDER 37 CFR § 1.132

1. We, Roland Martin and Henry McFarland, are the inventors of the above-identified patent application, along with Bibiana Bielekova. We were employed by the National Institutes of Health when the parent provisional application and parent PCT applications were filed.

2. It is our understanding that claims 1-9, 15-19, 21 and 29-31 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over "Study of Zenapax" in view of Light et al.

3. The Study for Zenapax was an abstract published to recruit patients for a clinical trial that we conducted at the National Institutes of Health. The trial design was as follows: Eleven patients with relapsing-remitting (RR) or secondary progressive (SP) multiple sclerosis (MS) were treated in this open-label baseline vs. treatment phase II trial. Inclusion criteria included the following: age 18–65 yr and expanded disability status scale (EDSS) 1.0–6.5. Exclusion criteria included the following: primary-progressive MS and concurrent medical conditions that could influence the immune system or accumulation of disability. Patients who were previously treated with therapies other than IFN-β had to discontinue these therapies for at

least 12 weeks. Failure to respond to IFN-β was defined as follows: at least one MS exacerbation or progression of sustained disability by at least 1 EDSS point during the preceding 18 months on therapy. Patients were followed by monthly clinical and MRI examinations on IFN-β monotherapy for 4 months. To initiate daclizumab dosing, we stipulated at least 0.67 new contrast enhancing lestions (CEL)/month during this baseline period. Daclizumab was administered intravenously at 1mg/kg/dose 2 weeks apart for the first 2 doses (month 0 & 0.5) and every 4 weeks thereafter for a total of seven infusions. MS exacerbations were defined by Schumacher's criteria and treated by intravenous methylprednisolone (IVMP) therapy (1 g/day x 5 days). MRI scans and clinical ratings within 28 days of IVMP were disregarded and substituted by data from the following month. Both baseline and treatment phases were extended appropriately by 1 month per MS exacerbation to yield 4 baseline and 6.5 treatment months that were not affected by IVMP.

Primary outcome measures were new CEL and total number of CEL at baseline (IFN-β) vs. combination therapy (IFN-β plus daclizumab). Secondary outcomes (MRI) were as follows: T2 lesion volume (T2LV), volume of CEL, and T1-hypointensities [black hole volume (BHV)]. Secondary outcomes (clinical measures) were as follows: exacerbation rate (cumulative number of exacerbations/cumulative baseline or treatment months), change in EDSS and Scripps Neurological Rating Scale (Scripps NRS), change in ambulation index, timed 25-foot walk, and 9-hole peg test (9-HPT), all baseline vs. treatment. The trial was approved by the National Institute of Neurological Disorders and Stroke institutional review board, and informed consent was obtained from every patient. A copy of the original protocol is attached as Exhibit B.

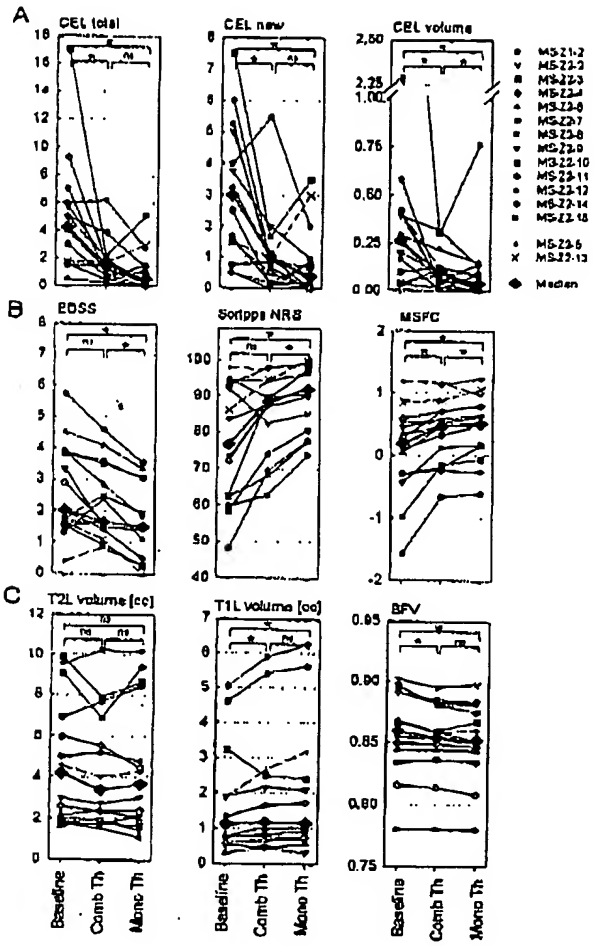
The results from this trial were published as *Bielekova et al., Proc. Natl. Acad. Sci.* 101: 8705-8708, 2004. A copy of Bielekova is attached as Exhibit A. Bielekova et al. conclude that "daclizumab add-on therapy represents a clear alternative to aggressive immunosuppression in MS patients with unusually high brain inflammatory activity that cannot be controlled by conventional immunomodulatory therapy. Positive experience regarding safety and efficacy has also been demonstrated in a separate cohort of secondary progressive-MS patients under open-label therapy." (see page 8707). Thus, the Study for Zenapax trial was conducted with daclizumab therapy "added on" to interferon beta. The conclusion from this study was that a combination of interferon beta and daclizumab could be used to effectively treat MS patients.

4. In order to evaluate whether Daclizumab alone maintains its therapeutic benefit in MS we performed a second open-label, baseline versus treatment phase II clinical trial of Daclizumab in MS. The protocol called for enrollment of 15 MS patients to yield at least 10 MS patients that finish the entire 17.5 months of Daclizumab dosing. The trial was approved by the NIH/NINDS institutional review board and shared with our originally reported trial (see paragraph 3, above) the same inclusion criteria; RR- or SP-MS, Age 18-65 years, expanded disability status scale (EDSS) 1.0-6.5 and suboptimal response to IFN-β defined as: at least 1 MS exacerbation/year or progression of sustained disability by at least 1 EDSS step in preceding 18 months. PP-MS patients and patients with concurrent medical conditions that could influence the immune system or accumulation of disability were excluded. All patients signed the informed consent and were followed by monthly clinical and MRI examinations. Before enrollment into the Daclizumab dosing phase, baseline MRI activity for each subject had to be at least 0.67 new CEL/month. MS exacerbations were defined by Schumacher's criteria and treated by IV methylprednisolone (IVMP; 1g/day x 5 days). MRI scans and clinical ratings within 28 days of IVMP were disregarded and substituted by data from the following month. The change in the number of new and total CEL between baseline (IFN-β) during the combination therapy (IFN-β+Daclizumab) and monotherapy (Daclizumab) treatment phases served as primary outcome measure. Secondary outcome measures included change in the volume of CEL, T2 lesion volume (T2LV), volume of T1 hypointensities (black hole volume; BHV), brain atrophy (Brain fractional volume, BFV) and change in clinical measures of disability: EDSS (from 0 = normal exam to 10 = death due to MS), Scripps Neurological Rating Scale (Scripps NRS; from 100 = normal exam to 0 = death due to MS) and MS functional composite (MSFC; calculated as z-score based on all collective baseline data in the cohort; higher number indicates improvement in disability). MRIs were acquired at 1.5 T using a standard protocol. CEL were recorded on hard copy films by consensus of two neuroradiologists. All volumetric analyses were performed by a single experienced rater using semiautomated thresholding techniques (PV-WAVE and MRIPS). Statistical differences between treatment periods were based on Friedman Repeated Measures Analysis of Variance on Ranks with predetermined P value < 0.05, using Student-Newman-Keuls procedure to correct for multiple comparisons.

Two patients did not complete the trial because of side-effects that we considered related to Daclizumab therapy. Only 1/15 patients (MS-Z2-11) did not reach the interim end-point of

decrease in CEL by 75% at month 5.5 of Daclizumab + IFN-β combination therapy and was put on double dose of Daclizumab + IFN-β with subsequent excellent therapeutic response. In 14/15 patients the IFN-β was withdrawn after 5.5 months, but in three patients we had to restart IFN-β due to sustained re-appearance of CEL lesions. Trial results (intention to treat analysis including all 15 subjects) are depicted in Figure 1. We observed 72% inhibition of new and 77% inhibition of total CEL by Daclizumab. Like in our original trial (see paragraph 3, above), this inhibition of CEL developed gradually and continued during dosing, such that the decrease in the volume of CEL reached statistical significance even when comparing combination therapy and monotherapy periods (Fig. 1a). Additionally, we observed a statistically significant improvement in all clinical measures of disability (Fig 1b). These measures continued to improve between combination therapy and monotherapy periods, arguing against reversal of transient, exacerbation-induced disability as a basis for this therapeutic response. We have not observed any significant changes in T2LV, and both BHV and BFV increased transiently between baseline and combination therapy but stabilized between combination therapy and monotherapy phases (Fig 1c).

Figure 1:



The data indicated that Daclizumab monotherapy was highly efficacious in 9/13 MS patients. The study results support the conclusion that Daclizumab monotherapy was a well tolerated and highly effective therapeutic option in patients with high-inflammatory MS with suboptimal clinical response to interferon beta. The steady and continuous recovery of the clinical deficit that we observed in this patient cohort suggests that Daclizumab therapy inhibits tissue injury by brain inflammation without interfering with the natural recovery process. Overall in the study, 15.5 months of Daclizumab therapy led to significant inhibition of MRI disease activity (by

72%) and to significant improvement in clinical disability. The unexpected superior results obtained in this study support the rapid development of this drug for MS patients with high inflammatory disease activity.

4. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Roland Martin, M.D.

Date

Henry McFarland, M.D.

1/14/07

Date